REMARKS

Claims 19-41 and 43-46 were pending prior to this response. By the present communication, no claims are added or cancelled and claims 19 and 40 have been amended to define Applicants' invention with greater particularity. The amendments add no new matter, the claim amendments being fully supported by the specification and original claims. Specifically, the support for the amendment to claim 19, may be found, among others, at page 18, lines 1-2. Accordingly, claims 19-41, and 43-46 are currently pending.

Rejection under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 19-41 and 43-46 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner alleges that the recitation of "normalizing the representation of organisms" is unclear because the specification fails to define the term "normalizing." Applicants respectfully direct the Examiner's attention to page 26, lines 4-12, as amended herein, in which Applicants describe one embodiment for forming a normalized library. Co-pending, commonly assigned U.S. Serial No. 08/665,565, the entirety of which is incorporated by reference, describes and exemplifies normalization in detail. Furthermore, at page 17, line 27 to page 18, line 2, Applicants indicate that "a normalization of the environmental DNA present in these samples could allow more equal representation of the DNA from all of the species present in the original sample." However, to reduce the issues, Applicants have amended claim 19 to better define the normalization step. Accordingly, Applicants submit that the meaning of the term "normalization" is clearly provided by the entire specification, and withdrawal of the rejection is respectfully requested.

The Examiner further alleges that claim 19 is indefinite as being incomplete because claim 19 does not list method steps for carrying out the "normalizing." Applicants respectfully direct the Examiner's attention to page 24, line 26 to page 26, line 12, and to Example 2 at page 68, in which Applicants have provided several embodiments for forming a normalized library. As such, one of skill in the art would understand the meaning of claim 19 as amended.

Accordingly, Applicants submit that the meaning of the term "normalization" is clearly provided by the entire specification, and withdrawal of the rejection is respectfully requested.

The Examiner further alleges that claim 19 is incomplete as it is unclear how the bioactive fluorescence is generated for clone identification. Applicants have amended claim 19 to indicate that the step of contacting occurs under conditions suitable for at least one clone to express a bioactivity or biomolecule of interest. Accordingly, Applicants submit that claim 19, as amended is clear, and withdrawal of the rejection is respectfully requested.

The Examiner further alleges that claim 19 is indefinite in the recitation of "naturally occurring DNA" as it is unclear as to the scope of DNAs that are intended as being "naturally occurring." As discussed in the response filed July 19, 2004, the plain dictionary meaning of the phrase "naturally occurring" is "as found in nature". This is, indeed, the meaning of the term as used throughout the Specification. While Applicants agree that genomic DNA that is cloned into a vector for purposes of creating a recombinant genomic DNA library has been manipulated, Applicants respectfully submit that claim 19 recites "normalizing the representation of organisms present *in a sample containing naturally occurring DNA*...." Applicants direct the Examiner's attention to the specification at page 25, lines 1-2, in which the first step of "normalizing" is "isolation of nucleic acid from the sample." Thus, it is the environmental sample that contains the naturally occurring DNA (i.e., DNA as found in nature). Although, once the DNA has been isolated, it has, by definition, been manipulated, it is still the same naturally occurring DNA as collected from the environmental sample. Accordingly, Applicants submit that the claim 19 clearly recites the scope of DNAs that are intended to be encompassed by the term "naturally occurring," and requests withdrawal of the rejection.

Finally, the Examiner alleges that claim 40 is confusing in the recitation of "a clone identified in step c)". Applicants have amended claim 40 to correct the step in claim 19 that refers to identifying clones. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claims 19-41 and 43-46 as failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph, for

allegedly introducing new matter. Specifically, the Examiner alleges that the disclosure provides support only for lower eukaryotic microorganisms and does not provide support for all eukaryotic organisms. Applicants respectfully direct the Examiner's attention to the specification at page 17, lines 20-28, in which environmental libraries are described as "represent[ing] the collective genomes of naturally occurring organisms archived in cloning vectors that can be propagated in suitable prokaryotic hosts. Because the cloned DNA is initially extracted directly from the environment, the libraries are not limited to the small fraction of prokaryotes that can be grown in pure culture." DNA representing the genomes of organism is, by definition, genomic DNA. An environmental sample includes any sample of DNA isolated directly from the environment (see specification at page 24, lines 1-5. It therefore stands to reason that an environmental sample containing naturally occurring organisms could contain DNA from any eukaryotic organism. Accordingly, Applicants submit that the specification provides support for all eukaryotic organisms, and requests withdrawal of the rejection.

The Examiner further alleges that support for the limitation "wherein each clone contains DNA from a single organism" is not found in the specification. Applicants respectfully direct the Examiner's attention to the Specification at page 29, lines 2-24, in which cloning DNA fragments is described. The process "lowers the probability of two DNA molecules ligating together to create a chimeric clone." Accordingly, Applicants respectfully submit that the subject limitation has support in the specification in compliance with MPEP 714.02 and 2163.06, and requests withdrawal of the rejection.

Rejection under 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 19, 20, 22, 24-29, 35, 37-39 and 43-45 under 35 U.S.C. § 102(b) as allegedly being anticipated by Thompson et al. (U.S. Patent 5,824,485; hereinafter "Thompson") as originally applied in the Office Action mailed herein December 07, 1999 and maintained in subsequent Office Actions. Applicants submit that the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, distinguish over Thompson at least by requiring:

a) normalizing the representation of organisms present in a sample containing naturally occurring DNA from more than one organism to allow equal representation of the DNA from all of the organisms present in the sample....

In the Specification, Applicants describe the effect of "normalizing" DNA in a sample as follows:

> The present invention can further optimize methods for isolation of activities of interest from a variety of sources, including consortias of microorganisms, primary enrichments, and environmental "uncultivated" samples, to make libraries which have been "normalized" in their representation of the genome populations in the original samples. and to screen these libraries for enzyme and other bioactivities. Libraries with equivalent representation of genomes from microbes that can differ vastly in abundance in natural populations are generated and screened. This "normalization" approach reduces the redundancy of clones from abundant species and increases the representation of clones from rare species. (Specification, page 24, lines 11-22).

Thus, the invention methods require preparation of a library in which representation of the various species from the original sample has been adjusted to equalize representation of organisms in the library.

Thompson is silent regarding "normalizing" DNA, as described by the present application, to allow more equal representation in a library of the DNA from the organisms present in the original sample. The Examiner alleges that Thompson's disclosure teaches a method for increasing the representation of non-ribosomal RNA sequences prior to producing the genomic DNA library of clones such that the abundant ribosomal RNA is reduced, thus increasing the representation of the remaining non-ribosomal sequences. However, Thompson's techniques would not result in equal representation of all of the organisms in the sample because Thompson discards samples with the largest amounts of ribosomal RNA. As stated at col. 40, lines 62-64 of Thompson, "[f]ollowing centrifugation, the samples containing the largest amounts of ribosomal RNA *can be discarded*, and the remaining fractions dialyzed and precipitated." (emphasis added). By contrast, Applicants do not discard the samples containing the largest amounts of representative nucleic acid. Applicants' normalization step allows *equal representation* of the DNA from *all* of

the organisms present in the sample. In short, Thompson fails to disclose any procedure by which the complexity of the DNA population isolated is analyzed and treated in such a way that *equalization* in copy numbers of clones in the mixed population is attained.

Accordingly, in view of Thompson's failure to disclose normalization of the species to allow equal representation of the DNA from all of the organisms present in the sample prior to screening, Applicants submit that Thompson fails to disclose each and every element of claims 19, 20, 22, 24-29, 35, 37-39 and 43-45 as would be required to establish anticipation under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

A. Applicants respectfully traverse the rejection of claim 23 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above).

The deficiencies of Thompson described above for disclosing the invention methods of claim 19 apply equally and are incorporated here with regard to claim 23, which depends from claim 19. In addition, Applicants respectfully submit that Thompson fails to suggest the invention methods and would not motivate those of skill in the art to modify Thompson to arrive at the presently presented invention methods because the thrust of Thompson's disclosure is devoted to preparation and screening of libraries in which the representation of clones has not

been normalized to allow equal representation of the DNA from all of the organisms present in the sample.

Specifically, Thompson's disclosure of utilizing uncultured organisms to make sure that the representation of organisms in the library is not skewed from that in the original sample and using "reconstituted metabolic pathways" does not suggest and would not motivate those of skill in the art to "normalize" the representation of organisms in the library to allow equal representation of the DNA from *all* of the organisms present in the sample, as described in Applicants' specification and claims. Thus, Applicants submit that Thompson's disclosure does not establish *prima facie* obviousness of the invention method of claim 23 under 35 U.S.C. § 103.

B. Applicants respectfully traverse the rejection of claims 30-32 and 34 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) and Miao et al, Biotechnology and Bioengineering (1993) 42:708-715, hereinafter "Miao".

Applicants' remarks above regarding the failure of Thompson to render obvious claim 19 and 23 apply equally and are incorporated here. In addition, Applicants submit that the disclosure of Miao fails to remedy the deficiencies of Thompson under 35 U.S.C. § 103 with regard to claim 19, from which claims 30-32 and 34 depend. Miao's disclosure pertains to use of C_{12}FDG as a fluorescent substrate in FACS screening of single bacterial cells of one species (i.e., *E. coli*). Thus, like Thompson, Miao is completely silent regarding screening of a library containing DNA that has been normalized to allow equal representation of the DNA from all of the organisms present in a sample.

Indeed, Miao's disclosure does not pertain to screening of a plurality of species, Applicants submit that the combined disclosures of Thompson and Miao would be insufficient to motivate those of skill in the art to create a method for "normalizing" the representation of organisms prior to creating the library to avoid to allow equal representation of the DNA from all of the organisms present in the sample. In addition, even if those of skill in the art were motivated by the combined disclosures of Thompson and Miao to arrive at the invention methods, Applicants submit that the cited art would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. Neither Thompson nor

Miao discusses any technique by which the DNA from the organisms of a sample is normalized to allow equal representation of the DNA from all of the organisms present in the sample prior to making a library. Therefore, those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson and Miao.

Accordingly, Applicants respectfully submit that the combined disclosures of Thompson and Miao, including Miao's disclosure regarding rapid screening using C_{12}FDG, are not sufficient to teach or suggest Applicants' invention of dependent claims 30-32 and 34, which contain the requirements of amended claim 19. Thus, Applicants respectfully submit that claims 30-32 and 34 are not *prima facie* obvious over Thompson, or the combined disclosures of Thompson and Miao.

C. Applicants respectfully traverse the rejection of claim 33 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) and Miao (as above) and further in view of Hirata et al. (U.S. Patent No. 4,861,718; hereinafter "Hirata").

Applicants submit that the remarks above regarding the failure of the combined disclosures of Thompson and Miao to render obvious the invention of claims 19 (and 30-32 and 34 dependent therefrom) under 35 U.S.C. § 103 apply equally and are incorporated here. The Examiner acknowledges that the combination of Thompson and Miao is not sufficient to block patentability of claim 33 under 35 U.S.C. § 103 (Office Action of October 9, 2003, page 13, bottom paragraph).

In addition, Applicants submit that the disclosure of Hirata fails to remedy the deficiencies of Thompson-Miao disclosure with respect to claim 19. Hirata's disclosure is relied upon by the Examiner as disclosing the heating of a nucleic acid encoding a thermostable beta-galactosidase having a temperature optimum at 70 degrees Celcius. However, like Thompson and Miao, Hirata is completely silent regarding screening of a library containing DNA that has been normalized to allow equal representation of the DNA from all of the organisms present in the sample.

Indeed, since Hirata's disclosure does not pertain to normalization of the representation of a plurality of clones in a library or to high throughput screening of a library of a plurality of

organisms, with each clone containing DNA from only one of the organisms, to determine fluorescence, as is required in amended claim 19, Applicants submit that the combined disclosures of Thompson and Miao and Hirata would be insufficient to motivate those of skill in the art to modify the combined disclosures to arrive at such a method at any temperature.

In addition, even if those of skill in the art were motivated by the combined Thompson-Miao-Hirata disclosures to arrive at the invention methods, Applicants submit that the cited art would fail to provide the reasonable expectation of success that is required to show obviousness under 35 U.S.C. § 103. Because none of the three references discusses any technique by which the DNA of organisms in a screening library can be normalized to allow equal representation of the DNA from *all* of the organisms present in the sample, those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined Thompson-Miao-Hirata disclosures. Thus, Applicants respectfully submit that claim 33 is not *prima facie* obvious over the cited art.

D. Applicants respectfully traverse the rejection of claims 21, 36, 40 and 46 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) in view of Minshull et al. (U.S. Patent No. 5,837,458; hereinafter "Minshull").

The remarks above regarding the failure of Thompson to render obvious under 35 U.S.C. § 103 the invention of claims 19 and 20, from which claims 21, 26, 40 and 46 depend, apply equally and are incorporated here. In addition, Applicants submit that the disclosure of Minshull fails to remedy the deficiencies of Thompson acknowledged by the Examiner with regard to the claims at issue (Office Action of October 9, 2003, page 15, second paragraph).

Minshull is relied upon for allegedly disclosing cellular and metabolic engineering by recursive sequence recombination. However, Applicants submit that the combined disclosures of Minshull and Thompson fail to disclose or suggest the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, due to failure of either reference to suggest procedures for normalizing the representation of organisms in the library to allow equal representation of the DNA from all of the organisms present in the sample.

In addition, Applicants submit that even if those of skill in the art were motivated by the combined disclosures of Thompson and Minshull to arrive at the invention methods, the combination of Thompson and Minshull would fail to provide the reasonable expectation of success that is required to show obviousness under 35 U.S.C. § 103. As neither Thompson nor Minshull discusses any technique for normalizing the representation of organisms in the library, Applicants submit that those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson and Minshull to arrive at such results. Accordingly, Applicants submit that *prima facie* obviousness of claim 33 is not established over the combined disclosures of Thompson and Minshull.

E. Applicants respectfully traverse the rejection of claim 41 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) in view of Minshull (as above) and further in view of Loveland et al. (*Appl Environ Microbiol* 60:12-18; hereinafter "Loveland").

The remarks above regarding the failure of the combined disclosures of Thompson and Minshull to render obvious under 35 U.S.C. § 103 the invention of claims 19 and 40, from which claim 41 depends, apply equally and are incorporated here.

In addition, Applicants submit that the disclosure of Loveland fails to remedy the deficiencies of Thompson acknowledged by the Examiner with regard to the claims at issue (Office Action of October 9, 2003, page 15, second paragraph). Loveland is relied upon for allegedly disclosing "isolation of a polynucleotide encoding a beta-galactosidase from a psychrotropic bacterium that exhibited a temperature optimum about 20 degrees Celsius below that of Escherichia coli beta-galactosidase" (Office Action, page 14). However, Loveland's disclosure pertains to isolation of an organism using techniques of amino acid analysis, enzyme test strips, and cell growth assays using ONPG as the substrate for testing for enzyme activity. At no point does Loveland disclose or suggest "isolation of a polynucleotide encoding [the enzyme]" as asserted by the Examiner.

Moreover, Applicants submit that the combined disclosures of Minshull and Thompson fail to disclose or suggest the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, due to failure

of any one of the references to suggest procedures for normalizing the DNA of organisms in a sample to allow equal representation of the DNA from all of the organisms present in the sample.

In addition, Applicants submit that even if those of skill in the art were motivated by the combined disclosures of Thompson, Minshull and Loveland to arrive at the invention methods, the combination of Thompson, Minshull and Loveland would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. As not one of Thompson, Minshull and Loveland discusses any technique for normalizing the representation of DNA of multiple organisms in the library, Applicants submit those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson Minshull and Loveland to arrive at such results. Accordingly, Applicants submit that *prima facie* obviousness of claim 41 is not established over the combined disclosures of Thompson, Minshull and Loveland.

In view of the above amendments and remarks, reconsideration and withdrawal of the various rejections under 35 U.S.C. § 103 are respectfully requested.

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Filed: June 16, 1997
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CONCLUSION

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge any and all fees that associated with this communication, including the fees to cover the Three-Month extension of time fee, or credit any overpayment to Deposit Account No. 50-0661.

Respectfully submitted,

Date: April 1, 2005

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